CHAPTER 38

Management of nausea and vomiting

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Marked progress in controlling chemotherapy-induced emesis has occurred over the past 10 to 20 years. Nonetheless, nausea and vomiting remain among the most distressing side effects of cancer chemotherapy. With the increased use of chemotherapy in primary and adjuvant treatment settings, the need for improved control of emesis remains an important consideration in both medical oncology and supportive care.

Over the past few years, several major oncology groups have published consensus reports or guidelines on the prevention of chemotherapy-induced emesis. However, the introduction of several new agents may change these paradigms. In addition, an understanding of the neuropharmacology of this problem is useful in planning patient care.

Pathophysiology of emesis

Although the mechanism by which cancer chemotherapy induces emesis is still not completely understood, a physiologic basis for our current understanding of this complex problem has now emerged.

Stimulation of neurotransmitter receptors

The emetic reflex arc is activated by stimulation of receptors in the CNS and/or GI tract. These receptor areas relay information to the vomiting center in the medulla, which then coordinates the act of vomiting. The chemoreceptor trigger zone (CTZ), also located in the medulla, serves as a "chemosensor" and is exposed to blood and CSF. These areas are rich in a variety of neurotransmitter receptors.

Dopamine For many years, the dopamine receptors were the main focus of interest in antiemetic research. Available antiemetics, such as phenothiazines (chlorpromazine and prochlorperazine) and substituted benzamides (metoclopramide), were known to affect these receptors, as were butyrophenones (haloperidol and droperidol).

Serotonin The role of the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) has also been elucidated. The improved antiemetic activity of higher doses of metoclopramide was not explained by its dopamine-binding properties, but by the fact that it also affects serotonin receptors. This led to the

development of several highly specific compounds that interact solely with serotonin receptors, specifically the type 3, or 5-HT_3, receptor subtype. Four compounds from this family are currently available. The 5-HT_3 receptor, which is found in both the GI tract and CNS, is an important mediator of the emetic reflex arc. Recent work has suggested that mutation of the 5-HT_{3B} receptor subunit may affect antiemetic efficacy.

Substance P Tachykinins, such as substance P, play an important role in emesis, as well as in pain and a variety of inflammatory conditions. These neurotransmitters are 11–amino acid molecules that bind to specific receptors. Substance P binds to the neurokinin type 1, or NK_1, receptor.

Several NK_1 receptor antagonists have been synthesized and used both preclinically and in clinical trials in patients receiving cancer chemotherapy. Results indicate that these agents are effective against a broad range of causes of emesis, particularly delayed emesis. One member of this family, aprepitant (Emend), has been approved for clinical use.

Emetic problems

Emesis related to chemotherapy

Both nausea and vomiting are seen in patients receiving cancer chemotherapy. Nausea occurs at a slightly higher frequency than vomiting and is more difficult to control. The control of vomiting is strongly correlated with the control of nausea, although some patients experience nausea without vomiting.

In patients receiving chemotherapy, several emetic problems have been identified. The three most common problems are outlined below.

Acute chemotherapy-induced emesis is defined as nausea or vomiting that occurs within the initial 24 hours of chemotherapy administration. The time of greatest risk is from 1 to 6 hours after chemotherapy with most agents.

Delayed emesis is emesis that begins ≥ 24 hours after chemotherapy. Delayed emesis is particularly likely to occur in patients who have received cisplatin, carboplatin (Paraplatin), or cyclophosphamide (Cytoxan, Neosar). Recent data indicate that this problem may begin somewhat earlier than 24 hours in some patients.

Anticipatory emesis is defined as a conditioned vomiting response following inadequate antiemetic protection with earlier courses of chemotherapy.

Emesis unrelated to chemotherapy

Patients receiving anticancer drugs may also develop emesis for other reasons. They include emesis induced by concomitant medications (such as analgesics, anti-infectives, or bronchodilators) or tumor-related complications (such as intestinal obstruction or brain metastases). In these instances, adjustment of medication or treatment of tumor-related complications is more important than selecting an antiemetic agent.

Patient characteristics and emesis

History of poor emetic control Poor control of emesis with past courses of chemotherapy predisposes a patient to unsatisfactory antiemetic results with any subsequent treatment, regardless of the emetic stimulus or antiemetic employed. Both delayed and conditioned anticipatory emesis are more likely to occur in these patients, and there is likely to be greater difficulty in controlling acute emesis.

History of alcohol intake Emesis is easier to control in patients with a history of chronic, high alcohol intake (> 100 g/d of alcohol [approximately five alcohol units or drinks]). In a prospective evaluation of 52 patients receiving high-dose cisplatin and an effective combination antiemetic regimen, 93% of those with a history of high alcohol intake had no emesis, as opposed to 61% of those without such a history. This difference in emesis control is independent of the patient's current alcohol intake.

Age Most trials have found that it is easier to control emesis in older patients than in younger ones. Younger patients have a predilection for developing acute dystonic reactions when dopamine-blocking antiemetics are administered (see section on "Antiemetic agents for high-emetic-risk chemotherapy"). Younger patients also have a greater tendency to develop anticipatory emesis than do older patients.

Gender It is more difficult to control emesis in women than in men given the same chemotherapy and antiemetic regimen.

Motion sickness Patients with a history of motion sickness are more likely to develop chemotherapy-induced nausea and vomiting than are those without such a history.

The above predisposing factors appear to be additive. One can identify patients at particularly high risk of emesis, such as younger women without a history of high alcohol intake. Awareness of these factors is helpful in monitoring individual patients and interpreting the results of clinical trials.

Chemotherapeutic agents and emesis

Emetic potential The most accurate predictor of the risk of emesis is the chemotherapeutic agent that a patient is receiving. Several different classifications of commonly used chemotherapy agents have been devised. Table 1 is based on the consensus report of the Multinational Association for Supportive Care in Cancer (MASCC) as updated in June 2004.

The emetic potential of a chemotherapeutic combination is determined by identifying the most emetic agent in the combination. Other agents in a combination may also increase the risk.

In general, agents that have the highest *incidence* of emesis also induce the most *severe* emesis. Differences occur among patients and even between identical treatment courses in the same patient. Both the dose and route of administration of the chemotherapeutic agent can affect the incidence of nausea and vomiting.

TABLE 1: Emetic potential of chemotherapy agents

Level	Frequency of emesis (%)[a]	Agent
High	> 90	Carmustine Cyclophosphamide (≥ 1,500 mg/m^2) Cisplatin Dacarbazine Hexamethylmelamine Mechlorethamine Procarbazine Streptozocin
Moderate	30-90	Carboplatin Cyclophosphamide (< 1,500 mg/m^2) Cytarabine (> 1,000 mg/m^2) Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide Irinotecan Oxaliplatin Temozolomide
Low	10-30	Capecitabine Cytarabine (≤ 100 mg/m^2) Docetaxel Etoposide Fluorouracil Gemcitabine Methotrexate (> 50 mg/m^2) Mitomycin Mitoxantrone Paclitaxel Pemetrexed Topotecan
Minimal	< 10	Bleomycin Busulfan Chlorambucil 2-Chlorodeoxyadenosine Fludarabine Hydroxyurea Melphalan Thioguanine Vinblastine Vincristine Vinorelbine

[a] Proportion of patients experiencing emesis in the absence of effective antiemetic prophylaxis

Time of onset of emesis In patients receiving initial chemotherapy of high emetic risk, nausea or vomiting typically begins between 1-2 hours after chemotherapy. Cyclophosphamide and carboplatin may be associated with a late onset of emesis (ie, 8-18 hours following chemotherapy administration).

Antiemetic agents for high–emetic-risk chemotherapy

Careful antiemetic research has shown that numerous agents are safe and effective. Dosage and administration schedules for some of these agents are given in Table 2. Antiemetic therapy can be administered either orally or intravenously.

Among the best studied agents are ondansetron (Zofran), granisetron (Kytril), dolasetron mesylate (Anzemet), palonosetron (Aloxi), metoclopramide, haloperidol, dexamethasone, aprepitant (Emend), lorazepam, dronabinol (Marinol), prochlorperazine, and chlorpromazine.

The efficacy and safety of palonosetron (Aloxi) in preventing chemotherapy-induced nausea and vomiting in elderly patients were assessed in a retrospective subset analysis of two randomized phase III studies. The subset consisted of 165 patients aged 65 years and older who received a single IV dose of palonosetron (.25 mg), ondansetron ([Zofran] 32 mg), or dolasetron ([Anzemet] 100 mg). Concomitant dexamethasone was administered to 3% of patients. A greater proportion of palonosetron-treated patients (n = 79) were free of emesis (77.2%) than patients (n = 86) treated with ondansetron/dolasetron (61.6%). Study investigators concluded that a single dose of palonosetron is more effective in preventing chemotherapy-induced nausea and vomiting over 5 days post chemotherapy in elderly patients (Aapro MS, Macciocchi A: Proc Am Soc Clin Oncol [abstract] 23:737, 2004).

The combination of a single prechemotherapy dose of a 5-HT_3 antagonist and dexamethasone is the most commonly used therapy to prevent emesis in patients receiving chemotherapy of high emetic risk (both cisplatin and noncisplatin) as listed in Table 1. Addition of aprepitant may increase the rate of antiemetic protection.

Serotonin antagonists: Ondansetron, granisetron, dolasetron mesylate, and palonosetron

Ondansetron, granisetron, dolasetron mesylate, and palonosetron are highly selective 5-HT_3 receptor antagonists. All are effective in controlling emesis induced by a variety of chemotherapeutic agents. Oral and IV routes of administration available for ondansetron, granisetron, and dolasetron mesylate are equally effective, as demonstrated in large randomized trials. In addition, single-dose regimens given before chemotherapy are as effective as more cumbersome multiple- or continuous-dose regimens.

All four serotonin receptor antagonists are similar with regard to efficacy and side effects, although palonosetron has a significantly longer half-life. Choice of one agent over another may therefore reflect economic or convenience factors as well as therapeutic index. Doses of these agents are given in Table 2.

TABLE 2: Dosage and administration schedules of antiemetic agents for acute emesis for chemotherapy of high emetic risk

Antiemetic agent	Dosage[a]	
	Oral	Intravenous
Dolasetron mesylate	100 mg once	100 mg (1.8 mg/kg) once
Granisetron	1 or 2 mg once	1 mg (0.01 mg/kg) once
Ondansetron	16-24 mg once or 8 mg bid	8 mg (0.15 mg/kg) once
Palonosetron	Not available	0.25 mg once
Dexamethasone	20 mg once	20 mg once over 5 min
Metoclopramide	Not recommended	2-3 mg/kg q2h
Haloperidol	1-2 mg q4-6h	1-3 mg q4-6h
Dronabinol	5 mg/m^2 q4h	Not available
Prochlorperazine	Not recommended	10-20 mg q3-4h
Lorazepam[b]	0.5-2.0 mg	0.5-2.0 mg q4-6h
Aprepitant	125 mg	Not available

[a] All agents are to be administered prior to chemotherapy, usually 30 minutes beforehand, although the serotonin antagonists can be effective if administered as late as immediately before the start of chemotherapy. Recommended dosages have been found to be effective in clinical trials and may vary from those given in package inserts.

[b] Lorazepam is indicated only as an adjunct to antiemetics in this setting.

Side effects Ondansetron, granisetron, dolasetron mesylate, and palonosetron have all demonstrated excellent safety characteristics over a large dosing range. Toxicities have been minor and have included headache, mild transient elevation of hepatic enzyme levels, constipation, and, with some agents, minor prolongation of cardiac conduction intervals.

Dystonic reactions and akathisia (restlessness), which may be treatment-limiting with antiemetic agents known to block dopamine receptors, are not seen with serotonin antagonists, even when given on consecutive days. This finding is of particular importance for younger patients, in that several regimens used to treat malignancies in this age group utilize a daily schedule of chemotherapy.

Efficacy The serotonin antagonists have been reported to achieve complete control of emesis in 30%-50% of patients receiving cisplatin. These agents have also proved to be at least as effective against all other chemotherapeutic agents, with complete control rates of about 70%.

Many trials have examined the benefit of adding corticosteroids to a serotonin antagonist. Typically, the complete control of emesis is improved by 10%-20% in patients receiving highly emetic chemotherapy. Both the American Society of Clinical Oncology (ASCO) and MASCC guidelines recommend that a corticosteroid be added whenever a serotonin antagonist is indicated (ie, in all patients receiving chemotherapy of high emetic risk).

Dexamethasone

The antiemetic mechanism of action of dexamethasone remains unclear. Several randomized trials and a recent meta-analysis have all confirmed its effectiveness in controlling emesis and its safety. Other corticosteroids are also effective; however, dexamethasone is the most widely studied steroid and is available in oral and parenteral dosage forms as an inexpensive generic product.

Dexamethasone is an excellent agent for use in combination antiemetic regimens and as a single agent for patients receiving chemotherapy of low emetic risk (< 30% incidence).

Dose Dexamethasone doses have generally ranged from 4 to 20 mg/d. In a randomized trial in patients receiving chemotherapy of high emetic risk, a single 20-mg dose was superior in completely controlling both nausea and vomiting. Thus, the 20-mg dose is recommended in this setting. For patients receiving chemotherapy of moderate emetic risk, a single 10-mg dose may be sufficient.

Side effects Toxicities associated with short courses of dexamethasone used for antiemetic therapy have been mild and generally consist of insomnia and mild epigastric burning. Care using this agent in patients with diabetes is particularly warranted.

Metoclopramide

Metoclopramide has proved to be safe and effective when given in high IV doses. Metoclopramide was thought to function as an antiemetic through blockade of dopamine receptors. However, high concentrations of this agent effectively block 5-HT_3 receptors as well.

Efficacy In patients receiving cisplatin, high-dose metoclopramide is an active antiemetic agent. However, randomized trials comparing metoclopramide with serotonin antagonists in high-risk settings have shown advantages for the latter agents. Metoclopramide is a second-choice agent, after the serotonin antagonists, in these settings.

Side effects Commonly observed side effects with metoclopramide include mild sedation, dystonic reactions, akathisia, anxiety, and depression. Dystonic reactions are age-related and route-related. In a report summarizing the experience of nearly 500 patients receiving metoclopramide, the incidence of trismus or torticollis was only 2% in those older than age 30; in contrast, a 27% occurrence was reported in younger patients. Also, such reactions are more common when metoclopramide is administered by the oral route or is given over several consecutive days.

Acute dystonic reactions are not allergic in nature. In general, dystonic reactions and akathisia can be prevented or easily controlled by administering diphenhydramine, benztropine mesylate (Cogentin), or a benzodiazepine. These reactions should not be viewed as a contraindication to further use of dopamine-blocking drugs.

In a multicenter, randomized, double-blind, phase III trial, 866 breast cancer patients being treated with cyclophosphamide (Cytoxan, Neosar) with or without doxorubicin (Adriamycin) or epirubicin (Ellence) were randomized to receive either a regimen of aprepitant (Emend, 125 mg), ondansetron (Zofran, 8 mg bid), and dexamethasone (Decadron, 12 mg) on day 1 with aprepitant (80 mg qd) on days 2 to 3; or a standard regimen of ondansetron (8 mg bid) on days 1 to 3 and dexamethasone (20 mg) on day 1. Of the 857 evaluable patients, 50.8% in the aprepitant arm, vs 42.5% (P = .015) in the standard regimen arm, achieved a complete response. In addition, more patients in the aprepitant arm achieved a complete response during both acute (75.7% vs 69.0%, P = .034) and delayed (55.4% vs 49.1%, P = .064) phases. Both treatments were generally well tolerated (*Warr DG, Eisenberg P, Hesketh PJ, et al: J Clin Oncol 22:730s, 2004 [suppl; abstract 8007]*).

Haloperidol

Haloperidol exerts its antiemetic action through dopaminergic blockade. A formal study comparing haloperidol with metoclopramide in patients receiving cisplatin found both agents to be effective, although metoclopramide afforded better emetic control.

Dose Haloperidol doses of 1-3 mg given IV q4-6h have been used.

Side effects Toxicities of haloperidol include sedation, dystonic reactions, akathisia, and occasional hypotension.

Lorazepam

Although lorazepam and other benzodiazepines are potent anxiolytic agents that can be useful additions to antiemetic therapy, they should not be used as single agents for chemotherapy-induced emesis. Lorazepam has been shown to achieve a high degree of patient acceptance and subjective benefit but only minor objective antiemetic activity. However, the anxiolytic properties of benzodiazepines may be particularly useful in the treatment of anticipatory nausea and vomiting.

Dose Lorazepam is usually given in doses of 0.5-1.5 mg/m^2 IV or 1-2 mg PO. These doses, especially the higher IV administrations, can be associated with marked sedation lasting for several hours.

Dronabinol and cannabinoids

Many trials have tested the antiemetic effects of dronabinol (delta-9-tetrahydrocannabinol [THC]), a component of marijuana. Dronabinol has modest antiemetic activity, similar to that seen with oral prochlorperazine.

Semisynthetic cannabinoids (such as nabilone) have been tested but appear to have no clear advantage over dronabinol. The modest antiemetic activity and significant toxicity of cannabinoids make them a second choice for the control of chemotherapy-related emesis.

Dose Dronabinol has been tried in many doses and schedules. The most useful doses have ranged from 5 to 10 mg/m^2 PO q3-4h.

Side effects are frequently associated with cannabinoids and are particularly bothersome in older adults. They include dry mouth, sedation, orthostatic hypotension, ataxia, dizziness, euphoria, and dysphoria.

TABLE 3: Antiemetic regimens for acute emesis by emetic risk

Risk level	Recommended antiemetic regimen[a]
High (cisplatin)	Serotonin antagonist
	plus
	Dexamethasone (12 mg)
	plus
	Aprepitant (125 mg)
High/moderate	Serotonin antagonist
	plus
	Dexamethasone (20 mg)
Low	Single agent, such as corticosteroid or serotonin antagonist
Minimal	No preventive agent is recommended for general use

[a] See Table 2 for doses.

Phenothiazines

Although phenothiazines were the first effective antiemetics, the results of antiemetic trials with this class of agents against highly emetogenic chemotherapy have been poor. Randomized trials have found standard-dose prochlorperazine, given orally or intramuscularly, to be less effective than metoclopramide or dexamethasone and equivalent to or less effective than dronabinol. IV administration is more effective than oral administration but can rarely cause profound hypotension (unlike serotonin antagonists or metoclopramide). Phenothiazines are seldom used as first-line antiemetic agents for highly or moderately emetogenic chemotherapy.

Side effects of phenothiazines include sedation, akathisia, hypotension, and dystonic reactions.

Aprepitant

Aprepitant is the first NK_1 antagonist antiemetic. NK_1 antagonists have demonstrated activity against a wide range of emetogenic stimuli. Although less effective than serotonin antagonists as single agents against acute emesis, NK_1 antagonists have shown superior activity against delayed emesis, suggesting the value of combination therapy.

Combination antiemetic regimens

Table 3 summarizes recommended antiemetic regimens, according to the emetic potential of the chemotherapy regimen.

Serotonin antagonist plus dexamethasone Combinations of a 5-HT_3 antagonist and dexamethasone form the basis of the most effective regimens for controlling acute chemotherapy-induced emesis. Use of these two agents combined has proved to be more effective than either agent alone. Addition of an NK_1 antagonist (aprepitant) results in increased activity against acute cisplatin-induced emesis.

Treatment of acute emesis

A management strategy to prevent acute chemotherapy-induced emesis is outlined in Table 3. All patients should receive education and reassurance, as well as antiemetics tailored to the chemotherapy regimen. For regimens that commonly cause emesis (> 30%), antiemetic combinations are recommended; for regimens of low risk (10%-30% incidence), a single agent will usually suffice. As stated in Table 3, chemotherapy of minimal risk typically does not require preventive treatment.

TABLE 4: Treatment regimens for delayed emesis

Risk level	Duration	Agent	Dose and schedule
High	Days 2-4	Aprepitant	80 mg PO qd x 2
		plus	
		Dexamethasone	8 mg PO qd
		Serotonin antagonist	
		Ondansetron	8 mg PO bid
		Dolasetron mesylate	100 mg PO bid
		Granisetron	1 mg PO bid
		[a]Palonosetron	0.25 mg IV day 1 only
		plus	
		Dexamethasone	8 mg PO bid
		Metoclopramide	30-40 mg PO bid
		plus	
		Dexamethasone	8 mg PO bid
Moderate	Days 2-3	Serotonin antagonist or dexamethasone or metoclopramide as single agent or in combination at dose and schedule above	
Low		No preventive regimen is recommended for general use	
Minimal		No preventive regimen is recommended for general use	

[a] Palonosetron has only been studied when given on day 1 with a single dose of dexamethasone (20 mg IV)

The rationale for treating high-risk patients receiving either cisplatin or other chemotherapy with the same serotonin antagonist doses is based on our current understanding of the neuropharmacology of emesis. Once all of the relevant receptors (5-HT_3) are saturated by the antiemetic, dose escalation will not be helpful. However, to achieve maximal benefit, it is necessary to give a dose that achieves this saturation. Thus, the lowest fully effective dose is the proper one for any chemotherapy-associated emetic setting in which a serotonin antagonist is to be given.

DELAYED EMESIS

Delayed emesis is defined as nausea or vomiting beginning or persisting ≥ 24 hours after chemotherapy administration. The pathophysiology of this problem is unclear, but it is particularly common after high-dose cisplatin (≥ 50 mg/m^2), carboplatin (≥ 300 mg/m^2), cyclophosphamide (≥ 600 mg/m^2), or doxorubicin (≥ 50 mg/m^2).

In one natural history study, 89% of patients experienced some delayed emesis from 24 to 120 hours after receiving high-dose cisplatin, with a peak incidence occurring between 48 and 72 hours. With anthracyclines or cyclophosphamide, the rate of delayed emesis without preventive antiemetics is about 30%.

Some observations suggest that delayed emesis may begin earlier. When combination antiemetic regimens for acute emesis "fail," the initial emetic episode is often at 17 to 23 hours following chemotherapy. In some trials, antiemetics to prevent delayed emesis have been initiated at 16 to 17 hours.

Treatment options The combination of oral dexamethasone and metoclopramide has been found to be superior to dexamethasone alone or placebo in a double-blind, randomized trial. The combination of dexamethasone and aprepitant has also demonstrated efficacy. The recommended doses and schedules for the prevention of delayed emesis are given in Table 4.

The majority of trials examining the role of 5-HT_3 antagonists as single agents in the control of delayed emesis have been disappointing. The 5-HT_3 receptor may be less involved in the pathophysiology of delayed emesis. Regimens combining a serotonin antagonist with dexamethasone can lessen delayed emesis (see Table 4 for dosages) and are comparable to metoclopramide and dexamethasone in activity but are markedly more costly. In moderate-risk settings, dexamethasone alone may be sufficient for many patients.

Perhaps the greatest single problem in antiemetic prescribing is the omission of dexamethasone in the prevention of acute and especially delayed emesis.

ANTICIPATORY EMESIS

This problem is defined as nausea or vomiting beginning before the administration of chemotherapy in patients with poor emetic control during previous chemotherapy. As this problem is a conditioned response, the hospital environment or other treatment-related associations may trigger the onset of emesis unrelated to chemotherapy. Strong emetic stimuli combined with poor emetic control increases the likelihood that anticipatory emesis will occur.

Treatment approach Behavioral therapy involving systematic desensitization can be helpful in managing anticipatory emesis. Also, benzodiazepines appear to be useful. However, the best approach to anticipatory emesis is prevention. This underscores the need to provide the most effective and appropriate antiemetic regimens with the initial course of emesis-producing chemotherapy.

SUGGESTED READING

Gralla R, Lichinitser M, Van Der Vegt S, et al: Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: Results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol 14:1570–1577, 2003.

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